UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JUL 27 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Two-year rat bioassay; Record no. 223459; EPA ID no. 53023-Q; Proj. No. 8-0880; Caswell No. 557C

TO: Dick Mountfort/C. Rice (PM 23)
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D. James N. Rowe 7/26/88
Section V, Toxicology Branch
Hazard Evaluation Branch (TS-769C)

THRU: Quang Q. Bui, Ph.D. Quang Q Bui 7/26/88
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Theodore M. Farber, Ph.D. 7/27/88
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

ACTION: Review of two-year rat bioassay (BASF Project No. 71S0045/8358); Record no. 223459; EPA ID no. 53023-Q; Proj. No. 8-0880; Accession Nos. 40634101-40634105; Caswell No. 557C

DISCUSSION/CONCLUSIONS:

Oral administration of MCPA (0, 20, 80, 320 ppm) for two years in the diet of male and female Wistar rats produced evidence of body weight depressions in males but not females; and hepato- and nephrotoxicity in both sexes at either the mid or high dose level. Hepatoxicity was evident primarily, in females, by statistically significant elevations in triglycerides (MDT,HDT) in both sexes, decreased cholesterol and increased clotting time in HDT females and increased SGPT levels (MDT, HDT) in females. Nephroxicity was indicated by increased absolute and relative kidney weights in HDT females associated with an elevation in blood urea concentrations. In HDT males, gross pathology in the kidneys was suggested by an increase in retraction and granularity of the kidneys associated with an increase in the chronic progressive nephropathy. There was no evidence of an oncogenic response in either male or female rats treated with MCPA under the conditions of the bioassay.

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The systemic toxicity NOEL is set at the low dose level (20 ppm) for both males and females based upon the hepatotoxicity and nephrotoxicity observed in either the mid and/or high dose groups. Oncogenic NOEL > 320 ppm (HDT).

CLASSIFICATION: This study is classified as Core Minimum data for both oncogenicity and chronic toxicity.

This study fulfills the data requirement for a two-year rodent study in the 1982 MCPA Registration Standard.

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Reviewed by by: James N. Rowe, Ph.D. James N. Rowe 7/26/88
Section V, Tox. Branch (TS-769C)
Secondary Reviewer: Quang Q. Bui, Ph.D.
Section V, Tox. Branch (TS-769C)

DATA EVALUATION RECORD

STUDY TYPE: Chronic/onco (2 yr rat) TOX. CHEM. NO: 557C

ACCESSION NUMBER: 40634101-40634105 MRID NO.:

TEST MATERIAL: 4-Chloro-2-methylphenoxyacetic acid

SYNONYMS: MCPA mix

STUDY NUMBER(S): 71S0045/8345

TESTING FACILITY: Department of Toxicology of BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG

TITLE OF REPORT: Report: Study on the Chronic Toxicity and Oncogenic Potential of MCPA in Rats

AUTHOR(S): P. Kirsch, Study Director

REPORT ISSUED: May 18, 1988

CONCLUSIONS:

Oral administration of MCPA (0, 20, 80, 320 ppm) for two years in the diet of male and female Wistar rats produced evidence of body weight depressions in males but not females; and hepato- and nephrotoxicity in both sexes at either the mid or high dose level. Hepatoxicity was evident primarily, in females, by statistically significant elevations in triglycerides (MDT,HDT) in both sexes, decreased cholesterol and increased clotting time in HDT females and increased SGPT levels (MDT, HDT) in females. Nephroxicity was indicated by increased absolute and relative kidney weights in HDT females associated with an elevation in blood urea concentrations. In HDT males, gross pathology in the kidneys was suggested by an increase in retraction and granularity of the kidneys associated with an increase in the chronic progressive nephropathy. There was no evidence of an oncogenic response in either male or female rats treated with MCPA under the conditions of the bioassay.

The systemic toxicity NOEL is set at the low dose level (20 ppm) for both males and females based upon the hepatotoxicity and nephrotoxicity observed in either the mid and/or high dose groups. Oncogenic NOEL > 320 ppm (HDT).

CLASSIFICATION: This study is classified as Core Minimum data for both oncogenicity and chronic toxicity.

A. Materials:

1. Test compound:MCPA mix (4-chloro-2-methylphenoxyacetic acid), Description 83/46; Batch # T.P.H. batch , Purity 94.8%.
2. Test animals: Species: rats, Strain: Wistar[Chbb = THOM (SPF)], Age at receipt: males, 29 days and females, 30 days; Weight: 1. Main group: males, 179 g (155-207), females, 134 g (116-151), 2. Satellite Group I: males, 177 g (158-198) and females, 139 g (120-160); Source: Dr. Karl Thomas GmbH, Biberach, Riss., FRG.

B. Study Design:

1. Animal assignment

Animals were assigned by randomization using a computerized system to the following test groups:

Test group	Dose in diet(ppm)	Main study 24 mos		Interim sacrifice* 12 mos (Satellite I)	
		male	female	male	female
1 control	0	50	50	10	10
2 low(LDT)	20	50	50	10	10
3 mid(MDT)	80	50	50	10	10
4 high(HDT)	320	50	50	10	10

* A second Satellite Group (Sat II) of 15 animals/sex/group was kept for clinical chemistry, hematology and necropsy after 24 months

2. Diet preparation

Diet was prepared at intervals of not more than 21 days and stored at room temperature. The homogeneity and stability of the test mixture in the maintenance diet was determined prior to study initiation and again at about 3 months after study initiation. Concentrations of the test material in the feed mix were determined at the beginning, 3, 6, 9, 12, 15, 18, 21 and 24 months.

Results-

The study report stated that the active ingredient content was determined to be 94.8% prior to study initiation, 95.6% after 1 year and 95.9% at study end. It was reported that storage of MCPA for 2 years at room temperature and at 30, 40 and 50°C had no effect upon purity.

Analysis of the stability of MCPA in diet mix indicated a range of 97-106% of nominal at day 0 and and 108-115% of nominal after 32 days of a sample prepared and stored at room temperature.

Homogeneity of samples (20, 320 ppm) analyzed at two intervals (3/84 and 6/84) indicated % of nominal values ranging from 97 to 118 (20 ppm) and 89 to 108 (320 ppm) for the first analyses; and 82 to 98 (20 ppm) and 88 to 90 (320 ppm) for the second set of analyses.

Mean concentration values, measured every 3 months, for all dose levels ranged from +/-10%, usually +/- 5% of nominal, during the exposure period.

3. Animals received food (Kliba rats maintenance diet, "A" 343 meal, KLINGENTALMUHLE AG, CH-4303 Kaiseraugst, Switzerland) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data:

a) Clinical examinations: Means and standard deviations were calculated for feed consumption, body weight and test substance intake; body weight was analyzed by ANOVA followed by a Dunnett's test

b) Blood and plasma: Following statistical adjustment using the NALIMOV criterion, the means and standard errors were calculated and the t test was used to compare individual dose groups with initial values (statistical significance = $p<0.05$ and 0.01)

c) Urinalyses: Chi^2 test with two-by-two contingency tables were used to compare control and test groups

5. Quality assurance was performed by the QAU for the study protocol, the conduct of study (15 inspections) and final report, with findings presented to the Study Director and Management. A signed statement to that effect by Dr. rer. nat. H. Fleig, dated May 16, 1988, was included.

C. Methods and Results:

1. Observations

Animals were inspected daily for signs of toxicity. A check was made twice/day Monday through Friday and once daily on weekends and holidays for mortality or moribund animals. In addition, they underwent inspection and palpation once a week.

Toxicity/mortality (survival)

A summary of selected clinical findings are presented below (taken from Tables T050-T053):

Findings:	0 ppm #: 50/15*	20 ppm 50/15	80 ppm 50/15	320 ppm 50/15
MALES				
Swellings in abdomen/ increased circumference of abdomen	4/2	5/2	7/5	8/2
Loss of hairs/sparse fur	0/0	0/0	0/1	3/0
Changes, tail/tailhead region	0/1	3/1	4/2	3/0
Conglutinations/colorations (e.g., area of snout, eye)	3/0	1/1	5/0	7/2
Conglutinations/colorations in lower abdomen	4/0	2/2	8/2	8/6
Deteriorated general state	9/0	4/1	8/3	15/3
FEMALES				
Swellings in abdomen/ increased circumference of abdomen	5/2	6/1	7/0	9/2
Loss of hairs/sparse fur	7/5	8/1	5/3	5/1
Changes, tail/tailhead region	1/0	0/0	0/0	0/0
Conglutinations/colorations (e.g., area of snout, eye)	7/0	9/2	4/0	5/3
Conglutinations/colorations in lower abdomen	2/1	1/0	2/1	1/1
Deteriorated general state	9/2	8/3	9/2	12/3

(* Main/Satellite group II, respectively)

Clinical signs of toxicity which appeared to be elevated in males at either the mid and high dose level were swellings in abdomen/increased abdominal circumference, loss of hair (HDT only), conglutinations/colorations of the snout, eye or lower abdomen and general deteriorated state (HDT only). Females appeared to have an increased incidence of abdominal swelling/

increased circumference in the mid and high dose groups and a slight increase in high dose animals with a deteriorated general health state.

Summary survival data (% of initial animal number) are presented below (taken from Tables T054 and T055):

MALES	d364	d637	d728	FEMALES	d364	d637	d728
Main							
0 ppm	100	88	78		100	86	72
20 ppm	100	90	76		96	80	76
80 ppm	98	84	62		100	84	72
320 ppm	100	88	72		100	76	64
SAT I							
0 ppm	100----------				90----------		
20 ppm	90----------				100----------		
80 ppm	100----------				100----------		
320 ppm	90----------				100----------		
SAT II							
0 ppm	100	87	67		100	100	67
20 ppm	100	87	60		100	93	80
80 ppm	100	100	67		100	87	80
320 ppm	100	80	67		100	93	87
Combined 0 ppm.....			75		.....		71
320 ppm.....			71		.....		69

There is no consistent evidence in either sex that MCPA administration affected the overall survival rate of the rats during the two-year exposure period. Combined animals from the main and satellite groups (Sat II) indicate equivalent cumulative mortality.

2. Body weight

Animals of the main groups and satellite groups were weighed once a week, including week 14 of administration; subsequently, body weight was determined at 4-weekly intervals. Body weights were determined on the same day of the week each time. Body weights were also determined at study termination.

Selected summary mean body weight data (g) are presented below: Minimal but statistically significant depressions in male mean body weights were observed early on (around day 14) and throughout the study period (3-9%) up to terminal sacrifice. In contrast, there was a small, sporadic but statistically significant elevation in female body weights in either the mid or high dose groups during the exposure period.

Males/main study

	d0	d14	d42	d77	d378	d714
G1	179.5	269.6	375.8	442.4	636.2	737.5
G2	180.0	266.6	369.1	439.3	648.9	710.1
G3	180.1	267.6	370.5	442.9	653.4	721.8
G4	176.0	261.0*	361.4*	427.6*	623.1	674.3*

Females/main study

G1	132.8	171.7	219.2	248.3	323.5	379.0
G2	134.0	175.8	226.3	257.7	328.6	387.4
G3	134.8	175.5	228.3*	260.4*	340.6	391.7
G4	133.6	172.7	222.0	253.8	343.0*	417.4*

G1, G2, G3, G4 = 0, 20, 80, 320 ppm; * statistically significant at $p<0.05$ (ANOVA = Dunnett's test)

3. Food consumption and compound intake

Food consumption of the main and satellite I groups were determined weekly up to and including week 14 and thereafter at 4-week intervals and at study termination. Mean food consumption/day/animal and mean amount of ingested test substance (mg) per kg body weight were determined at the same interval as food consumption.

Values given for test material intake represent a group mean calculated from the amounts ingested per individual animal using the following formula:

$$\frac{FC \times D}{BW_x}$$

FC = mean daily feed consumption (g) within one week of study (from day x-7 to day x), D = dosage in ppm, BW_x = mean body weight(g) on day x of study

Food consumption/compound intake

Selected mean food consumption and compound intake data are presented below:

MCPA administration did not produce any apparent effect upon general mean food consumption in either males or females during the exposure period.

Average substance intake increased, as expected, with the dose levels administered in male and females. Average MCPA intake over time diminished, as expected due the relatively stable daily food consumption in relation to continued increased body weights, in the various dose groups. Average mean MCPA intake in the main and satellite (Sat I) groups were similar.

Males/main study: FOOD CONSUMPTION DATA (g/animal/day)

	d7	d378	d714
G1	25.7	26.8	26.5
G2	25.8	27.4	26.0
G3	25.8	27.3	26.1
G4	25.3	27.0	25.3

Females/main study

G1	18.7	19.6	20.8
G2	18.9	20.0	21.6
G3	18.9	20.3	21.3
G4	18.8	20.9	21.4

G1, G2, G3, G4 = 0, 20, 80, 320 ppm

Males/main study: SUBSTANCE INTAKE (mg/kg bw)

	Selected data			Average over study period	
	d7	d378	d714	Main group	Satellite I
G2	2.3	0.8	0.7	1.1	1.3
G3	9.2	3.4	2.9	4.4	5.1
G4	36.7	13.9	12.0	17.6	20.4

Females/main study

G2	2.4	1.2	1.1	1.4	1.6
G3	9.6	4.8	4.3	5.7	6.4
G4	38.7	19.6	16.9	23.0	25.5

G2, G3, G4 = 20, 80, 320 ppm, respectively

4. Ophthalmological examinations

Performed on animals in control and high dose levels of main group for changes in refracting media using a focusable hand-held slit lamp before study initiation and about every 6 months during subsequent study period.

There was no evidence that MCPA produced a compound-related effect in the high dose group as compared with control animals.

5. a. Hematology

Blood was collected before treatment and about 26, 52, 78 and 104 weeks after the start of test material administration. Hematology and clinical analysis from 15 animals/sex/dose group in satellite group II were performed. For blood sampling 4, the satellite group II was supplemented with 15 animals per test group and sex from the main group animals. For hormonal analyses, blood was taken after 52 weeks from 10 animals/sex/dose group from satellite group II. The checked (X) parameters were examined:

X	
X hematocrit (HCT)*	X leukocyte differential count *
X hemoglobin (HGB)*	X mean corpuscular HGB (MCH)
X leukocyte count(WBC)*	X mean corpuscular HGB conc. (MCHC)
X erythrocyte count (RBC)	X mean corpuscular volume (MCV)
X platelet count*	X reticulocyte count
blood clotting measurements	
-thromboplastin time	
-clotting time	
X -prothrombin time	

* required for subchronic and chronic studies

Selected mean hematology values are presented below:

DOSE(PPM)		0 WEEKS	52 WEEKS	104 WEEKS
0	HQT:	------	40.520/35.100[a]	34.287/29.493
20	(sec)	------	40.785/35.347	35.847/30.960
80		------	41.293/35.423	35.640/30.667
320		------	38.847/35.900	35.679/31.647*
0	HT:	0.330/0.327	0.397/0.372	0.383/0.382
20	(L/L)	0.327/0.320	0.400/0.379	0.392/0.361**
80		0.332/0.329	0.408/0.374	0.381/0.358**
320		0.330/0.326	0.398/0.377	0.395/0.364**
0	THROMBO:	1016.133/1175.000	934.000/938.866	961.666/996.133
20	(giga/L)	1054.571/1105.636	957.071/871.266	1044.714/895.999*
80		1023.846/1044.428	996.200/934.357	1058.428/915.357
320		1045.333/1163.230	994.384/940.285	988.499/946.666
0	LEUKO:	7.843/7.121	5.746/4.183	5.463/4.968
20	(giga/L)	7.567/6.236	5.593/4.206	6.741*/4.433
80		7.773/6.545	5.835/3.981	7.531*/4.905
320		7.461/7.368	5.080/4.301	6.166/4.522

[a] male/female values
*,** Statistically significant ($p<0.05$, 0.01, respectively);
HQT = Hepato Quick's test (clotting time), HT = hematocrit,
THROMBO = platelets, LEUKO = leukocytes

A minimal elevation in clotting time, HQT, (statistically significant at both weeks 78 (data not presented) and 104; $p<0.01$) in high dose females was observed as compared to controls.(e.g. wk 104, 31.65/HDT vs 29.49 sec/control). In females, but not males, treated with MCPA, there was a statistically significant depression in hematocrit in all dose groups as compared with the control group at study termination (0.382/control vs 0.361/LDT, 0.358/MDT and 0.364/HDT). However, it should be noted that the changes in hematocrit were not observed in the 26 or 78 week sampling periods. There were no consistent changes in thrombocytes or leukocytes, although some statistically significant results were reported.

5.b. Clinical Chemistry (x indicates analyzed for)

Electrolytes:	Other:
X calcium*	X albumin*
X chloride*	X blood creatinine*
magnesium*	X blood urea nitrogen*
X phosphorus*	X cholesterol
X potassium*	X globulins
X sodium*	X glucose*
Enzymes	X total bilirubin*
X alkaline phosphatase	X total serum protein*
cholinesterase#	X triglycerides
creatinine phospho-kinase*@	serum protein electrophoresis
lactic acid dehydrogenase	
X serum alanine aminotransferase (also SGPT)*	
X serum aspartate aminotransferase (also SGOT)*	
gamma glutamyl transferase (GGTP)	
glutamate dehydrogenase	
X Triiodothyronine (T3)	
X Thyroxine (T4)	

* required for subchronic and chronic studies
# should be required for OP: plasma, erthrocyte ChE conducted 2X prior to study initiation, 3 and 6 mos. and prior to terminal sacrifice@ not required for subchronic studies

Selected clinical chemistry values are presented below:

DOSE(PPM)		0 WEEKS	52 WEEKS	104 WEEKS
0	UREA:	6.526/6.823[a]	7.486/7.724	7.056/6.888
20	(mmol/L)	6.026/6.728	7.586/7.724	7.078/6.857
80		5.986/6.700	7.512/7.866	7.106/7.066
320		6.024/6.590	7.111/8.382*	7.363/7.186
0	TRIG:	1.266/1.650	5.102/5.624	6.077/6.432
20	(mmol/L)	1.217/1.683	4.015/4.349	4.671/6.684
80		1.275/1.690	4.528/3.861*	4.023*/6.113
320		1.351/1.873	3.581/3.377**	3.936**/6.227

(continued from previous page)

0	CHOL:	2.351/2.149	2.654/3.061	3.651/4.227
20	(mmol/L)	2.100*/2.118	2.598/2.675	3.361/3.442
80		2.315/2.194	2.786/2.796	3.410/3.993
320		2.173/2.131	2.584/2.706	3.772/3.257*
0	GPT:	1.241/1.036	0.850/0.870	0.811/0.788
20	(uKAt/L)	1.305/1.127*	0.973**/0.913	0.785/0.854
80		1.321/1.041	1.047**/0.972**	0.835/0.801
320		1.437**/1.064	0.951/1.040**	0.912/0.917*
0	GOT:	2.024/1.814	1.530/1.379	1.405/1.463
20	(uKat/L)	2.159/1.855	1.618/1.382	1.486/1.492
80		2.056/1.895	1.503/1.478	1.539/1.715
320		2.288/1.713	1.668/1.672*	1.491/1.755

*, ** Statistically significantly different from concurrent control ($p<0.05$, 0.01, respectively)

Blood urea values in HDT males as compared to controls were somewhat depressed (not statistically significant) at 0, 26, 52 and 78 weeks but not 104 weeks. HDT female urea concentrations were consistently (statistically significant) elevated as compared to controls at 26, 52 and 78 weeks of analysis and remained somewhat elevated at 104 weeks.

Consistent decrements in triglycerides were noted in both treated males and females during the study period. In males, statistically significant decreases in triglycerides were observed in the mid and high dose groups at 78 (not shown) and 104 weeks of exposure. Mid and high dose females also showed decreases at 52 weeks (statistically significant) and 78 weeks (statistically signficant only at HDT) but not at 104 weeks.

No consistent changes in treated males for cholesterol were noted. HDT females had small but consistently lower cholesterol values at 52, 78 and 104 weeks (statistically significant at 104 weeks).

No consistent elevations in SGPT values were observed for treated males; females had consistent elevations in the mid and high dose groups as compared to controls at 52, 78 and 104 weeks (statistically significant for last two periods of analysis). No consistent findings for SGOT in either treated males or females were observed.

No changes in hormonal concentrations of T3 and T4 (not presented in table) were noted.

6. Urinalysis

Urine was collected from each animal overnight from the satellite group I at about 26 and 52 weeks from study initiation and from 10 main group animals/sex/dose group at about 104 weeks. Checked (X) parameters were examined.

X	X
appearance*	X glucose*
volume*	X ketones*
specific gravity*	X bilirubin*
X pH	X blood*
X sediment (microscopic)	X nitrite
X protein*	X urobilinogen

* required for chronic studies

No compound-related changes were noted for any of the urinalyses parameters evaluated including pH, sediment, protein, glucose, ketones, bilirubin, blood, nitrite and urobilinogen.

7. Sacrifice and pathology-
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organ in addition were weighed.

X	X
Digestive system	Cardiovascular/hematopoietic
-tongue	X-aorta*
X-salivary glands*	XXheart*
X-esophagus*	X-bone marrow*
X-stomach*	X-lymph nodes*
X-duodenum*	X-spleen*
X-jejunum*	X-thymus*
X-ileum*	Urogenital
X-cecum*	XXkidneys*[1]
X-colon*	X-urinary bladder*
X-rectum*	XXtestes*[1]
XXliver*[1]	-epididymides
-gall bladder*@	X-prostate
X-pancreas*	-seminal vesicle
Respiratory	XXovaries*[1]
X-trachea*	X-uterus*
X-lung*	Neurologic
-nose#	XXbrain*[1]
-pharynx#	X-peripheral nerves*@
-larynx#	X-spinal cord (3 levels)*@
	X-pituitary*
	X-eyes (optic n.)*@
Glandular	
XXadrenals*	
-lacrimal gland*@	
X-mammary gland*@	
-parathyroids*2	
X-thyroids*2	
Other	
X-bone*@	
X-skeletal muscle*@	
X-skin*@	
X-all gross lesions and masses*	

* required for subchronic and chronic studies
# required for chronic inhalation studies
@ in subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
1 organ weights required in subchronic and chronic studies
2 organ weights required for non-rodent studies

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a. organ weight

Selected organ weights(g)/relative organ weights (% of body weight) are presented below:

	0 ppm	20 ppm	80 ppm	320 ppm
MALES: Liver				
Sat I	16.26(1.938)[a]/ 2.85(0.282)	17.31(2.194)/ 2.93(0.210)	17.74(2.691)/ 2.97(0.306)	16.93(1.894)/ 2.98(0.321)
Sat II + Main	18.92(3.503)/ 2.85(0.429)	18.39(2.660)/ 2.91(0.400)	18.31(2.308)/ 2.85(0.376)	17.91(3.335)/ 2.82(0.359)
MALES: Kidney				
Sat I	3.16(0.253)/ 0.56(0.058)	3.39(0.222)/ 0.58(0.050)	3.32(0.384)/ 0.56(0.072)	3.57*(0.480)/ 0.63(0.081)
Sat II + Main	3.98(0.412)/ 0.61(0.072)	3.98(0.551)/ 0.63(0.109)	4.12(0.482)/ 0.64(0.100)	4.13(0.502)/ 0.65(0.109)
FEMALES: Liver				
Sat I	10.06(1.728)/ 3.32(0.247)	9.70(1.252)/ 3.02(0.232)*	9.93(1.289)/ 3.23(0.271)	9.11(0.877)/ 2.95(0.161)**
Sat II + Main	12.38(1.793)/ 3.61(0.411)	11.95(1.968)/ 3.50(0.359)	12.66(2.269)/ 3.58(0.486)	12.01(2.042)/ 3.33(0.389)**
FEMALES: Kidney				
Sat I	2.07(0.260)/ 0.69(0.098)	2.10(0.171)/ 0.66(0.059)	2.08(0.290)/ 0.68(0.081)	1.97(0.206)/ 0.64(0.065)
Sat II + Main	2.68(0.272)/ 0.79(0.119)	2.74(0.318)/ 0.80(0.131)	2.87(0.378)*/ 0.81(0.105)	2.83(0.324)/ 0.79(0.108)

[a] mean (standard deviation); *, ** statistically significant ($p<0.05$, 0.01)

No consistent changes in male liver or kidney weights were observed at any dose level of MCPA administered. HDT female absolute and relative liver weights were slightly but consistently depressed (statistically significant for relative weights) in the Sat I and combined Sat II/main study groups. No apparent changes in absolute or relative female kidney weights were observed.

b. Gross pathology

Selected gross findings from the report are presented below for the main study groups (satellite findings of possible concern are so indicated):

Observation (male/female) (# animals[a]):	0 ppm 50	20 ppm 50	80 ppm 50	320 ppm 50
Liver				
-focus	35/26	33/28	35/23	32/18
Kidneys				
-retraction	4/1	5/2	3/3	8/1
-granular surface	5/2	5/3	6/4	9/3
Testes				
-focus	5/-	12/-	11/-	9/-
-organ size reduced	9/-	9/-	10/-	7/-
-organ size reduced (Sat II)	1/-	2/-	4/-	4/-
Ovaries				
-cyst	-/11	-/19	-/13	-/9
Uterus				
-thickening of wall	-/2	-/6	-/12	-/9
Pituitary				
-enlarged	1/8	4/9	3/16	2/20
Adrenal				
- enlarged	6/11	3/10	5/17	5/23

[a] # animals for Sat II group = 15/dose group

Retraction and granular surface of the kidney in HDT males appear to be a MCPA-related gross change (i.e., 4/50 and 5/50 in controls vs 8/50 and 9/50 in HDT, respectively). Enlargement of the pituitary and adrenals in HDT females also appears to be a compound-related finding (i.e., 8/50 and 11/50 in controls vs 16/50 and 23/50 in HDT, respectively).

c. Microscopic pathology

1) Non-neoplastic

Selected non-neoplastic lesions from the main and Sat I groups are presented below:

Observation (male/female) (# animals):	0 ppm 50	20 ppm 50	80 ppm 50	320 ppm 50
MAIN GROUP				
Liver				
-spongiosis hepatis	19/1	23/3	24/2	27/3
-cholangiofibrosis	9/5	7/4	12/2	14/1
Lungs				
-calcification	3/2	3/-	5/1	6/1
Kidneys				
-tubular nephrosis	-/1	-/2	1/-	1/4
-hyperplas. pelv. epith.	1/2	3/5	1/-	4/3
-nephropathy, chr-prog	49/46	49/47	46/49	47/45
Testes				
-Leydig cell hyperpl.	16/-	15/-	8/-	24/-
Spleen				
-storage, hematog. pigm	19/37	17/31	27/26	27/36
Mesenteric lymph n.				
-hyperplas., lymphoret.	16/17	21/15	16/17	26/18
Pituitary gland				
-sinus ectasia	8/2	8/6	3/6	15/3
SAT I				
Kidneys				
-nephropathy, chr-prog	10/4	10/10	10/8	10/5
Spleen				
-storage, hematog. pigm	10/10	9/10	9/10	10/10
Mandibular lymph n				
-retic. cell hyperplas	-/1	-/5	3/4	-/6

Common non-neoplastic lesions seen in all dose-groups of both sexes were spongiosis hepatis of the liver, chronic progressive nephropathy, storage of hematogenous pigment in the spleen and lymphoreticular hyperplasia of the mesenteric lymph nodes. Testicular Leydig cell hyperplasia and sinus ectasia of the male rats were frequently observed findings but there was no clear evidence overall in the total animals examined (main, Sat I and II) of a dose-response effect of MCPA. The Leydig cell hyperplasia is not associated with any evidence of a compound-related increase in Leydig cell tumors.

A further breakdown of the kidney and spleen lesions is noted below. In males, there is evidence of an increased incidence of more severe grades of chronic progressive nephropathy in the HDT

Grading of chronic progressive nephropathy/pigment storage in spleen:

Observation (male/female) (# animals):		0 ppm	20 ppm	80 ppm	320 ppm
	Main	50	50	50	50
	Sat I	10	10	10	10
Kidneys -nephropathy, chr-prog					
Sat I	Grade				
	1	9/3	5/9	5/6	2/4
	2	1/1	5/1	5/2	2/1
	3	-/-	-/-	-/-	6/-
Main	Grade				
	1	9/27	----------		14/30
	2	21/12	----------		13/10
	3	16/5	----------		11/2
	4	3/2	----------		7/2
	5				2/-
Spleen -storage, hematog. pigm					
Sat I	Grade				
	1	7/2	6/6	7/3	3/1
	2	3/8	3/4	2/6	5/6
	3	-/-	-/-	-/1	2/3
Main	Grade				
	1	15/25	----------		22/20
	2	3/11	----------		4/15
	3	1/1	----------		1/1

as compared to controls. There is also a weak suggestion of an increased severity of hematogenous pigment accumulation in HDT females.

2) Neoplastic

Selected neoplastic lesions from main, Sat I and Sat II test groups are presented below:

Observation (male/female) (# animals):		0 ppm	20 ppm	80 ppm	320 ppm
	Main	50	50	50	50
	Sat I	10	10	10	10
	Sat II	15	15	15	15
MAIN					
Liver					
-hepatocell. adenoma		13/5	15/2	12/6	15/4
-hepatocell. carcinoma		3/-	1/-	1/1	4/-
-cholangioma		2/7	3/6	1/6	2/4
Testes					
-Leydig cell tumor		21/-	20/-	22/-	14/-
Mammary glands					
-adenoma		-/6	-/2	-/2	-/2
-cystadenoma		-/5	-/7	-/9	-/6
-fibroadenoma		-/12	-/9	-/13	-/17
-adenocarcinoma		-/5	-/-	-/7	-/4
Adrenal medulla					
-pheochromocytoma		19/7	11/8	20/7	18/9
Thyroid					
-adenoma		1/1	-/-	1/-	-/4
Pituitary gland					
-adenoma		13/26	15/26	11/28	10/28
SAT I					
Mammary glands					
-fibroadenoma		-/-	-/-	-/1	-/1
Spleen					
-hemangioma		-/-	-/-	-/-	-/1
Mandibular lymph n.					
-hemangioma		-/-	-/-	-/-	1/-
SAT II					
Testes					
-Leydig cell tumor		3/-	2/-	4/-	1/-
Mammary glands					
-fibroadenoma		-/1	-/1	-/1	-/1
Spleen					
-hemangioma		-/-	2/-	1/-	-/-
Adrenal medulla					
-pheochromocytoma		2/2	2/-	3/-	2/1

There is no clear evidence of an oncogenic response in either male or female dose groups treated with MCPA. Mammary gland fibroadenomas were somewhat elevated in the HDT over the controls in the main dose group or satellite groups (18/65, HDT vs 13/65,

control) but not in lower dose levels. A relatively high incidence of mammary gland fibroadenoma (20.6%) has been reported in female Wistar rats controls (Barsoum et al., Tox. Path., Vol. 12 (1): 26-38, 1984). Thyroid adenoma was somewhat higher in females rats of the HDT (4/50, HDT vs 1/50, control). However, this lesion was not observed in male animals of the main group, nor in the two satellite groups (either sex) and was not statistically significant by the Fisher's Exact test ($p<0.181$).

D. Discussion

Administration of MCPA mix in the diet of male and female Wistar rats in a subchronic oral study (0, 50, 150 and 450 ppm) resulted in hepatic (prolonged clotting times, decreased cholesterol concentrations) and kidney (increased absolute and relative weights, decreased serum calcium, increased creatinine) changes in either sex at the mid and/or high dose levels (Study No. 50S0045/8342). The systemic NOEL was set at 50 ppm.

The two-year oral rat study (0, 20, 80, 320 ppm) presently under review is in agreement with the findings of the subchronic study in terms of the general pattern of toxicity manifested. That is, the liver and kidney appear to be the target organs for MCPA-related toxicity. Although the findings are generally of a mild nature, they nevertheless support the rationale for the dose levels selected for the purposes of obtaining a MTD.

MCPA produced small but statistically significant depressions in mean body weights of HDT males but not females. No effects upon food consumption were observed in either sex, therefore the depressed body weight is considered a direct compound-related effect. No compound-related effects upon cumulative survival in either sex was noted.

Hepatoxicity was observed in both sexes, but primarily in females. Mid and high dose males and females had statistically significant elevations in triglycerides. HDT females had decreased cholesterol levels and increased clotting times while both mid and high dose females had increased SGPT levels.

Nephrotoxicity is also suggested in HDT females and possibly males. There was a statistically significant increase in absolute and relative kidney weights in HDT females associated with an increase in blood urea concentration. Gross pathology suggested an increase in the retraction and granular surface of HDT males, this was associated in HDT males with an increase in the severity of chronic progressive nephropathy (CPN) in the non-neoplastic histopathology.

There is no clear evidence of oncogenicity in either male or female dose groups treated with MCPA.

END